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**PEMOLINE AND METHYLPHENIDATE:  
INTERACTION WITH MOOD, SLEEPINESS, AND COGNITIVE  
PERFORMANCE DURING 64 HOURS OF SLEEP DEPRIVATION**

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Performance During 64 Hours of Sleep Deprivation**

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## ABSTRACT

Moderate doses of the stimulant drugs methylphenidate (10 mg every 6 hr x 8 doses) or pemoline (37.5 mg every 12 hr x 4 doses) were tested for their ability to maintain performance in a variety of cognitive tasks during 64 hr without sleep. Drug administration began at 2200 hr on the first evening of sleep deprivation. Testing occurred approximately every three hr. Reductions in performance speed and accuracy were a function of both the amount of prior wakefulness and of the hour of the day. The greatest changes occurred between midnight and 0600 hr, especially on the second night of sleep loss. At the doses used, pemoline was more effective than methylphenidate in countering the effects of sleep loss and the circadian cycle. The pemoline group showed less sleepiness on both subjective and objective measures. Neither drug had an effect on moods as measured by the Profile of Mood States (POMS). Pemoline significantly maintained performance speed above that of the placebo group on five of six tasks. The effect of pemoline on performance accuracy was more complicated. On two of the tasks pemoline had no effect on accuracy. On one task there was a significant improvement in accuracy. On one task there was a tendency ( $p < .1$ ) toward improved accuracy. On one task there was a tendency ( $p < .1$ ) toward greater deterioration. On one task (logical reasoning) accuracy deteriorated significantly more with pemoline than without. The complicated picture may be due to (a) differences in the cognitive function tested and its interaction with the drug or (b) the relative effectiveness of stimulants on the stimulus evaluation versus the response selection processes in a cognitive task.

## INTRODUCTION

During the past 50 years, laboratory and field research have regularly documented varying degrees of decrement in performance and changes in psychological variables during sleep deprivation. The decrements are dependent upon contextual, subjective, and environmental factors as well as the type of stimulus to which the subject responds (Babkoff, Mikulincer, Caspy, Kempinski, & Sing, 1988; Horne, 1988; Johnson, 1982). Sleep deprivation research involves manipulation and disruption of a naturally occurring physiological and behavioral rhythm, the sleep-wake cycle (Horne, 1988; Minors & Waterhouse, 1981; Monk, 1982; Sing, Thorne, Hegge, & Babkoff, 1985). It is not clear which effects of sleep deprivation relate to accumulating fatigue and which to interference with basic human rhythmicity. The ramifications are complicated by the fact that most of the physiological, psychological, and performance variables measured during such studies are themselves subject to rhythmic variations (mostly circadian), as well as the effects of sleep loss (Sing et al., 1985). Thus, there are two major sources of variance in performance during sleep deprivation: a predominantly monotonic factor related to accumulating fatigue and a cyclic factor related to endogenous rhythms.

Obviously, the best treatment for sleep deprivation and circadian disruption is sleep on a normal schedule. Various alternative remedies have been suggested. Napping or very short sleep periods have been proposed and tested as possible amelioratives for long periods of disrupted or decreased sleep (Dinges, Orne, Evans, & Orne, 1981; Dinges, Orne, & Orne, 1985; Dinges, Orne, Orne, & Whitehouse, 1986; Naitoh & Angus, 1989). The effectiveness of such measures remains unclear.

Various types of pharmacological interventions are being examined as potential agents for countering sleep deprivation-related performance degradation, although the practical issues in using drugs are many and include side effects as well as the possibility of abuse (Holliway, 1974; Krueger, 1989). This research has fallen into two general classes: using medications to prevent performance degradation or using them to reverse degradation once it has occurred.

Pharmacological research directed at prevention of performance deterioration during sleep deprivation usually involves the use of hypnotics to assure adequate sleep preceding a prolonged work period (O'Donnell et al., 1988; Spinweber, 1986). Stimulant drugs have most often been investigated as a remedy to counter the performance effects of fatigue after they have occurred,

rather than as a preventive measure. While there is some evidence that stimulants can elevate various types of performance above baseline in non-fatigued subjects, a substantial portion of the performance effects of these drugs appears to derive from reversal or prevention of the effects of fatigue related to sleep deprivation or boredom (Spiegel, 1979; Weiss & Laties, 1962). Recent reports indicate that certain stimulants can successfully recover performance after 48 hr of sleep deprivation (Newhouse et al., 1989).

However, stimulants might also be useful as a prophylactic measure, administered during periods of sleep loss prior to the appearance of performance decrement to prevent or delay the deterioration which would otherwise become manifest. The present study tested stimulants in a behavior maintenance paradigm, attempting to prevent decrements in performance and mood during 64 hr without sleep.

Methylphenidate and pemoline were selected as established strong stimulants worth investigating as possible alternatives to amphetamines. These drugs have been used extensively in attention deficit disorder and narcolepsy (Conners & Taylor, 1980; Mitler, Shafrazi, Hajdukovic, Timms, & Browman, 1986). Both drugs have shown evidence of reversing the effects of fatigue on performance (Gelfand, Clark, Herbert, Gelfand, & Holmes, 1968; Haward, 1970; Orzack, Taylor, & Kornetsky, 1968).

Methylphenidate is a piperidine derivative that is thought to activate the brain stem arousal system and the cortex. The usual medical dosage is 20 to 30 mg per day in divided doses (Barnhart, 1992).

Pemoline is an oxazolidine compound thought to act primarily through catecholamine uptake inhibition in the central nervous system (Molina & Orsingher, 1981). Its longer half life (approximately 12 hr vs 2 hr for methylphenidate) allows it to be used with less frequent dosing (Barnhart, 1992). While pemoline generally has to be given for a period of time before full benefit is seen in medical treatment (Barnhart, 1992), significant amelioration of performance degradation by fatigue has been reported after a single dose in normal adults (Haward, 1970; Orzack et al., 1968), as is true for methylphenidate (Gelfand et al., 1968). The effective medical dose of pemoline usually falls between 56.25 and 75 mg per day, administered in a single dose (Barnhart, 1992).

Research into the effects of pharmacological agents on cognitive processes has begun to

emphasize two major questions: Are there specific cognitive processes that are affected by certain drugs and not by others? What neurotransmitter systems are responsible for the effects of drugs on cognitive component processes (Callaway, 1983; Halliday, Callaway, & Lannon, 1989)? One experimental approach involves use of the Human Information Processing model of cognition. This model localizes the site of drug action by separately assessing the interaction of pharmacological agents with the stimulus evaluation and response selection components of tasks (e.g., Halliday et al., 1989; Naylor, Halliday and Callaway, 1985).

Many stimulants, including methylphenidate, have been reported to increase response speed on cognitive performance tasks. Does this increased speed relate to effects on stimulus evaluation or response processing? Manipulating stimulus and response complexity, Naylor et al. (1985) showed the drug effect increased as response complexity increased but was not affected by stimulus complexity. They interpreted the data to mean that methylphenidate affects response selection rather than stimulus processing. Additional support for this interpretation was adduced with the finding that neither response complexity nor methylphenidate affected the P300 latency of the event-related potential, although increasing stimulus complexity did increase P300 latency. In general, stimulants have been shown to have little effect on the mid-to-late latency of event-related potentials (P300) recorded during the task (Brumaghim, Klorman, Strauss, Levine, & Goldstein, 1987; Coons et al., 1981; Fitzpatrick, Klorman, Brumaghim, & Keefover, 1988; Naylor et al., 1985). Since P300 is associated with evaluating the stimulus in a task, the lack of interaction of stimulants with this component would imply that the mode of action is subsequent to stimulus evaluation processing.

In the Naylor et al. (1985) study, two findings argue for specificity of action on the response rather than on the stimulus component of the task: a) the interaction of methylphenidate with an intra-task variable (task complexity) and b) the presence of a behavioral effect without any change in a physiological variable associated with stimulus processing. While pemoline has not been studied as extensively and such data are not available for that agent, it has been proposed that stimulants in general act on response processing (e.g., response decision, selection, and execution), whereas barbiturates and cholinergics interact with stimulus processing (Callaway, 1983; Halliday, Callaway, Naylor, Gratzinger, & Prael, 1986).

In the present study pemoline and methylphenidate were administered on a maintenance schedule, starting the first night of a 64-hr period without sleep, to test their ability to prevent performance and mood degradation.

## METHOD

### Subjects

Thirty-six male students from the U. S. Navy Special Warfare training program volunteered to participate in this study. This population has previous experience with prolonged sleep deprivation. All subjects were medication free. The mean age was 20.94 years  $\pm$  2.75 years (range 18-28 years). Subjects were non-tobacco users because consumption of nicotine, a putative stimulant, would have confounded the effects of the medications. Heavy caffeine users, defined as those drinking more than 3 cups of caffeinated beverages per day, were excluded because the effects of withdrawal of caffeine might also have confounded the effects of the medications. All subjects gave informed consent after receiving a detailed explanation of the protocol, which had been approved by the Naval Health Research Center Committee for the Protection of Human Subjects.

### Procedures

The 36 subjects were randomly assigned in equal numbers to one of three groups in a parallel-group, double-blind design. The control group ( $N=12$ ) received placebo capsules every 6 hr for a total of 8 capsules. The methylphenidate group ( $N=12$ ) received 10 mg doses of methylphenidate every 6 hr for a total of 8 doses. The pemoline group ( $N=12$ ) received 37.5 mg doses of pemoline every 12 hr for 4 doses, with placebo capsules given at alternate 6-hr intervals. To test stimulant medications for possible future use in the field as a non-therapeutic measure in healthy individuals, it was felt that no more than standard medical doses should be used. However, standard medical administration is designed to affect the 16-hr wake period but not the 8-hr sleep period. Because there were no sleep periods in this study, the doses were adjusted proportionally to cover the full 24-hr period. Drug or placebo administration in all groups commenced at 2200 hr on the first night of sleep deprivation.

Two to 4 subjects at a time participated in each experimental run. Subjects remained in the laboratory 4 days while participating. Watches and clocks were not available to subjects during the study. However, the room where subjects spent time during breaks did have windows, so they had cues as to time of day. The testing room had standard low-level artificial light of an intensity well below that known to have circadian phase setting or alerting effects in humans. Regular meals of roughly equivalent nutritional/caloric value were provided to all subjects. However, subjects were not required to eat all of their food, and snack foods (e.g., potato chips) were allowed during breaks, so food consumption was not uniform. Other putative stimulants (e.g., coffee, tea, nicotine, and chocolate) were excluded from the diet during the study. No food was allowed for 2 hr before and 1 hr after medication administration. Figure 1 summarizes the experimental schedule.

On Monday, the first day of the study, subjects learned and practiced the computerized cognitive testing during the morning. In the afternoon, the first baseline test was performed. Practice continued through the rest of the day. Subjects slept in the laboratory Monday night, and the sleep deprivation period commenced at 0620 hr Tuesday morning. They remained awake, with about 2 hr of cognitive testing every 3 hr, until 2230 hr Thursday night. Subjects were constantly monitored by technicians who woke them if they fell asleep. Vital signs (blood pressure, pulse, temperature), mood, and subjective and objective sleepiness were also measured.

#### Vital signs

Blood pressure and pulse were recorded every 2 hr with a Critikon Dinamap vital signs monitor. Temperature was concurrently recorded with an oral basal temperature thermometer.

#### Subjective sleepiness

The Visual Analog Scale (VAS) for Alertness/Sleepiness was used to measure subjective sleepiness. Subjects were told to move a pointer along a 30-point continuum ranging from very sleepy to very alert to indicate their current level of sleepiness/alertness. VAS was measured every 3 hr during the 64 hr of sleep deprivation.

**FIGURE 1: STUDY SCHEDULE**

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
00-01	Sleep	Sleep			Recovery Sleep
01-02			Snack	Snack	
02-03					
03-04			Tsks/VS/Tsks	Tsks/VS/Tsks	
04-05			Med*/Break	Med*/Break	
05-06			VS/Tasks	VS/Tasks	
06-07			Break	Break	
07-08			Sleep Q/VS	Tasks/VS	
08-09			Shower/Brkfst	Shower/Brkfst	
09-10		Check-in			
10-11			BLT/VS/BLT	Tsks/VS/Tsks	Sleep Q/Symp Q Shower/Brkfst
11-12				Tsks/VS/Tsks	
12-13			Break	Med*/Break	
13-14	Lunch	Lunch	VS/BLT	VS/Tasks	Debrief
14-15			Break	Break	
15-16	Task Training	Task Training	BLT/VS	Tasks/VS	
16-17			Break	Med*/Break	
17-18			VS/BLT	VS/Tasks	
18-19	Dinner	Dinner	Break	Break	
19-20			BLT/VS	Tasks/VS	
20-21	Task Training	Free	Dinner	Dinner	
21-22					
22-23	Sleep	Sleep	Med*/Break	Med*/Break	
23-24			Tasks/VS	Tasks/VS	

Sleep Q. - Sleep Questionnaire  
 BLT - Baseline Computer Tasks  
 Tsks - Computer Tasks

Med\* - Medication  
 Symp Q. - Symptom Questionnaire  
 VS - Vital Signs

### **Objective sleepiness**

The Lapse task is a tapping task adapted from a similar task that was shown to correlate significantly with sleep latency as measured by the Multiple Sleep Latency Test (Johnson, Spinweber & Gomez, 1990). Subjects sat in a comfortable chair with their eyes open, their preferred arm supported, and their index finger resting on the response key. They were instructed to relax, stay awake, and to tap at the rate of about once per second. Task duration was 10 min. A lapse was scored when the interval between taps was more than 3 s. When intervals longer than 10 s occurred without a tap, the computer beeped to awaken or remind the subject to continue tapping. The tapping task was administered every 6 hr.

### **Mood**

Mood was measured by a computerized version of the POMS (McNair, Lorr, & Droppleman, 1971). The subscales of the POMS were used to measure degree of Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, Confusion-Bewilderment, Positiveness, and Total Mood Disturbance. POMs presents the subject with a series of words describing mood. The subjects were told to respond using a 5-point scale by typing a number from 0 to 4 describing how closely each word describes their current mood: not at all (0), a little (1), moderately (2), quite a bit (3), extremely (4).

### **Cognitive Tasks**

Analysis of the following performance tasks are presented in this article.

Matrix. The cognitive operations thought to be utilized in the Matrix task (Walter Reed Performance Assessment Battery [PAB]; Thorne, Genser, Sing, & Hegge, 1985) are vigilance, pattern recognition, and short-term memory. Subjects are required to observe a pattern of 14 stars presented for 2 s and to remember the pattern during an intervening 5-s blank screen period. When a second pattern is presented subsequently, the subject must determine whether it is the same or different. When the second pattern is not the same, it differs from the first pattern only in that 3 of the 14 stars appear in randomly selected new positions. There is no time limit on the response. The second pattern remains on the screen until the subject responds. Task duration is 20 min. Measures include number of trials, percent correct, mean correct

reaction time (RT), and mean incorrect RT.

Addition. The two-column Addition task (Walter Reed PAB; Thorne et al., 1985) measures the ability to perform simple addition problems with speed and accuracy. Because the sum must be completed mentally and then entered left to right, there is also a component of short-term memory. Subjects are presented with a series of addition problems. Each problem consists of 5 two-digit numbers. As soon as the first digit of the answer is entered, the problem disappears from the screen. There is no time limit for responding. The task lasts 20 min. Measures include number of problems attempted and percent correct.

Four-Choice Reaction Time. The Four-Choice Reaction Time task is a psychomotor task (Wilkinson & Houghton, 1975). On each trial a star is displayed at one of four positions. The four stimulus positions form a square. The response buttons are also arranged in a square, and the subject is required to press the button whose position corresponds to that of the star. The task is subject-paced, with each stimulus displayed until the subject presses a button. Subjects are tested with their preferred hand. The task lasts 11 min. Measures include number of responses, percent correct, and mean correct and incorrect RTs.

Digit Span. The Digit Span task assesses short-term memory capacity. A string of four random numbers is presented for 5 s. After the string disappears, the subject is required to type in the numbers from memory. If his answer is correct, another string of five numbers is presented. Each time a correct answer is given, the string length is increased by one number. If an incorrect answer is given, another string of the same length is presented. When two incorrect answers in a row are given, the task ends. The score is computed as follows: number of correct responses - 0.3 X number of incorrect responses (excluding last two).

Digit Symbol Substitution (DSS). The DSS task assesses associative memory and perceptual speed. The numbers 1 through 9 are displayed at the top of the screen randomly paired with the symbols !, @, #, \$, %, ^, &, \*, and (. Numbers are presented one at a time in the lower portion of the screen. The subject is instructed to press the key with the matched symbol. The numbers are presented randomly, with the limitation that no stimulus is presented twice in a row. The task lasts 5 min. Measures include the number of problems completed, the percent correct, and the average time per problem.

Logical Reasoning. The Logical Reasoning task is a computerized variation on the

Baddeley task (Baddeley, 1968). It measures the higher mental processes of reasoning, logic, the integration and manipulation of information, and verbal ability. Our version of this task uses sequences of three letters (A, B, and C, in any order) paired with two logical statements (e.g., "A follows B, C precedes A," paired with "BAC") with the response being T (true) only if both statements correctly describe the letter sequence [e.g., F (false) in the preceding example]. The random problem generator is adjusted so that half the problems are true and half are false. This is a self-paced task lasting 20 min. Measures include number of problems attempted and percent correct.

All of these tasks were presented once every 3 hr. Tasks of a set length (Matrix, Addition, DSS, and Logical Reasoning) varied slightly in actual administration time because, if the subject was working on a problem when the time ran out, the task did not end until he entered the answer to that problem. Matrix and Addition were administered in the first half of each session; Four-Choice RT, Logical Reasoning, Digit Span, and DSS were administered in the second half, with a 10-min break between the halves.<sup>1</sup>

### Statistical Analysis

Data were first analyzed by analysis of variance (ANOVA) for repeated measures covering the 48 hr of drug administration [Stimulant Group(S)(3) X Day(D)(2) X Hour of Day(H)(8)]. As an exploratory study with a small number of subjects, we have reported trend ( $.05 < p \leq .1$ ) as well as significant ( $p \leq .05$ ) findings from the ANOVAs. Subsequently, differences were further tested with post hoc Duncan Multiple Range tests. The level of significance for all post hoc analyses was set at  $p \leq .05$ .

One subject in the methylphenidate group who was found to be an extreme outlier (e.g., a 20-min Addition session during which only two problems were completed and only one was correct) was excluded from all of the analyses. A subject from the placebo group was also excluded because he had missing data on multiple sessions of all tasks except Four-Choice RT due to equipment failure. An additional placebo subject had missing data for the Addition tasks during the baseline trials, so there were only 10 placebo subjects (33 total subjects) in the baseline analysis for that task.

The statistical package (BMDP, P4V) corrected for unequal Ns and used

Geisser-Greenhouse epsilon corrected degrees of freedom (DF) to avoid inflated alpha with repeated measures. Each task ANOVA covered two 24-hr periods, 8 sessions per 24 hr, starting with the 2230 session on Tuesday after the first drug administration and ending with the last session on Thursday (1945). The vital signs ANOVAs had 12 measures per 24 hr. The large number of zeros (sessions with no lapse) in the lapses data produced a distribution significantly different from the Guassian. Therefore, these data were analyzed by the nonparametric Kruskal-Wallis test.

## RESULTS

### Vital Signs

ANOVAs performed on the pre-drug baseline trials showed no significant group differences on any of the vital signs. The ANOVAs on the post-drug trials reveal significant effects for H for systolic blood pressure [ $F(7.35,205.84)=5.26, p<.0001$ ], diastolic blood pressure [ $F(6.90,193.30)=3.26, p=.0029$ ], pulse [ $F(6.96,194.96)=35.79, p<.0001$ ], and temperature [ $F(5.47,103.88)=35.01, p<.0001$ ] consistent with circadian variation, i.e., highest 1220 hr to 1820 hr and lowest 0020 hr to 0620 hr. Diastolic blood pressure showed a significant group effect [ $F(2,28)=4.50, p=.02$ ]. Post hoc comparisons ( $p<.05$ ) indicated that the pemoline group had higher diastolic blood pressures than both the placebo and methylphenidate groups on 3 trials and that they were higher than one of these groups on an additional 8 trials. ANOVAs of systolic blood pressure, mean blood pressure, and rate pressure product showed no significant group differences. Pulse data showed an S x H interaction [ $F(13.93,194.96)=2.61, p=.0018$ ]. Post hoc analyses indicated that the only significant group difference for pulse was that the pemoline group showed a higher pulse rate than the methylphenidate group at 1435 hr on the second day of drug administration.

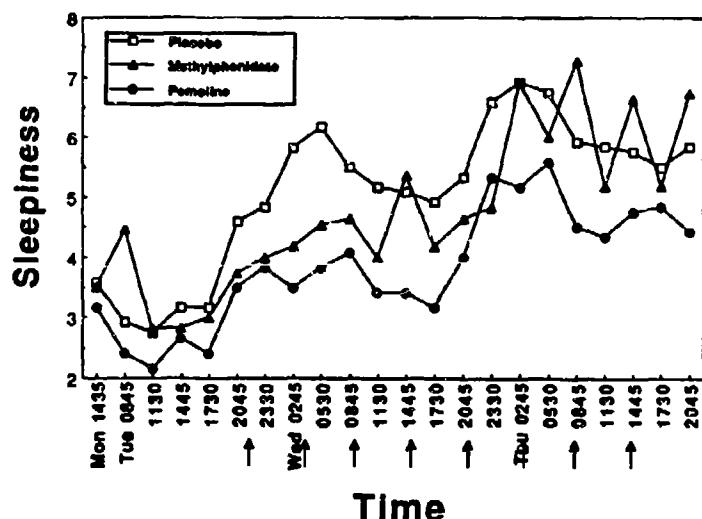
### Sleepiness and Mood

Subjective sleepiness ratings are plotted in Figure 2. Times of capsule administration are marked with arrows below the Time axis on this graph and on graphs in subsequent Figures. It should be recalled that the pemoline group received active drug only in every other capsule.

The ANOVA indicated trends for an S effect [ $F(2,32)=3.02, p=.06$ ] and an S x H interaction [ $F(7.96, 127.30)=1.79, p=.08$ ] for VAS sleepiness ratings. Post hoc analysis

demonstrated that only pemoline reduced subjective sleepiness, predominantly during the circadian troughs (0200 hr - 0600 hr). Subjects receiving pemoline were significantly less sleepy than subjects receiving placebo on both the first night [ $t(21) = -2.35, p < .03$ ] and the second night [ $t(22) = -2.05, p < .025$ ]. Subjects receiving pemoline were significantly less sleepy than subjects receiving methylphenidate during the second night [ $t(19) = -2.32, p < .04$ ] and during the afternoon (1300 hr - 1400 hr) on both the first [ $t(19) = -2.37, p < .03$ ] and second [ $t(18) = -2.27, p < .04$ ] days of drug administration.

**Figure 2: SUBJECTIVE SLEEPINESS**

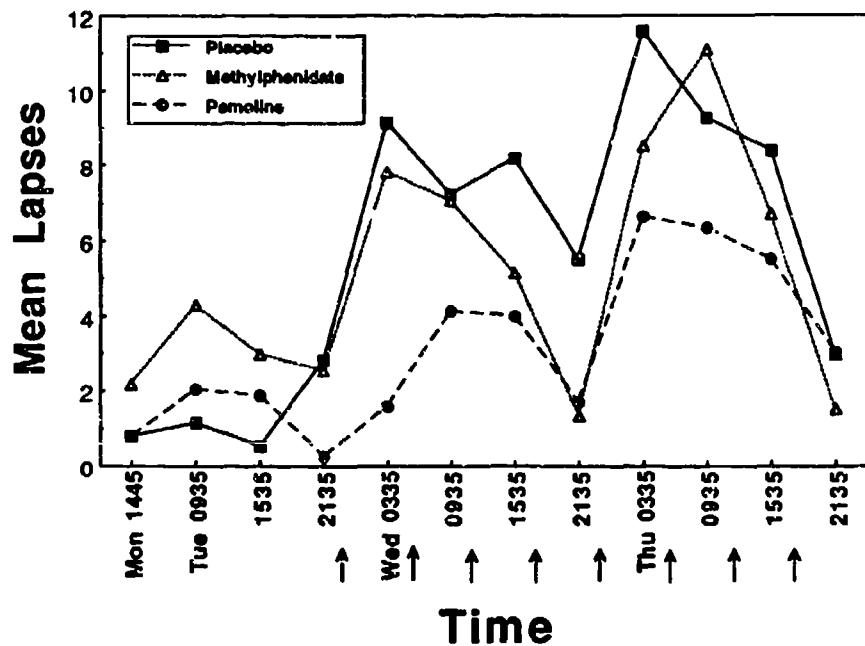


The objective sleepiness measure, the tapping task, is plotted in Figure 3. Results of the Kruskal-Wallis analysis of the tapping task indicated that there were significant S differences [ $H(34) = 6.55, p < .04$ ]. Paired group comparisons showed that subjects receiving pemoline ranked significantly lower in the number of lapses than subjects receiving methylphenidate [ $H(23) = 5.88, p < .02$ ]. The most pronounced drug effect occurred at the circadian trough of the first night when subjects who received pemoline had significantly fewer lapses than subjects who received methylphenidate [ $H(22) = 9.38, p < .002$ ]. A similar trend was found with the

pemoline versus placebo comparison [ $H(23) = 3.24, p < .07$ ]. Subjects receiving pemoline also ranked lower in the number of lapses than subjects who received placebo during the afternoon of the last day [ $H(23) = 3.89, p < .05$ ].

Neither main effects nor two-way interactions with drug were found for any of the subscales of the POMS.

**Figure 3: OBJECTIVE SLEEPINESS**



#### Baseline Performance on Cognitive Tasks

ANOVAS on the pre-drug trials revealed no baseline group differences except the number of problems per session in the Addition task, which showed a main effect for S [ $F(2,30) = 4.68, p = .0149$ ]. Placebo subjects performed a mean of 70 problems per session in the baseline trials ( $SD = 18$ ); pemoline subjects performed 56 problems ( $SD = 9$ ); and methylphenidate subjects performed only 48 problems ( $SD = 20$ ). To correct for this, the Addition speed scores were normalized by subtracting the baseline (average of Sessions 3, 4, 5, and 6) from the number of problems for each session. This was done to prevent a drug effect from being obscured or falsely indicated based on group differences which were present at baseline, prior to drug administration.

### Sleep Deprivation and Circadian Effects

Significant differences ( $p \leq .05$ ) and trends ( $.05 < p \leq .1$ ) suggesting effects of sleep loss and circadian rhythm on performance by ANOVA are summarized in Table 1. Both speed and accuracy measures from all of the tasks, except for the Digit Span, were sensitive to progressive sleep loss as measured by changes from the first 24 hr of drug treatment (D1) to the second 24 hr of drug treatment (D2). Every measure except Logical Reasoning accuracy showed a main effect for H representing circadian changes across the hours of the day. In addition, half the measures showed interactions between D and H.

### Drug Effects

Significant differences ( $p \leq .05$ ) and trends ( $.05 < p \leq .1$ ) suggesting drug effects on performance, and the interaction of these effects with those of sleep loss and circadian rhythm as demonstrated by ANOVA, are summarized in Table 2. Post hoc analysis showing the times of significant ( $p \leq 0.05$ ) group differences over the sleep deprivation period are presented in Table 3. Because Matrix and Addition were administered in the first half of each session and Four-Choice RT, Logical Reasoning, and DSS were administered in the second half, the entries for the latter three tasks are an hour later. For example, results from 0430 hr and 0530 hr are from the same session. Effects on speed and accuracy differed and are presented separately.

#### Drug Effect: on Speed

Response speed results are graphed in Figures 4 and 5. Figure 4 shows number of items attempted per session. Because the Addition scores had to be corrected for baseline differences between groups, the baseline period is not included in the Addition graph. Figure 5 shows correct and incorrect RT on the two tasks for which those measures were available.

As can be seen in Table 2, only the speed measures on the Matrix task showed significant main effects for S [number attempted:  $F(2,31)=7.26$ ,  $p=.0026$ ; correct RT:  $F(2,31)=5.01$ ,  $p=.0130$ ; incorrect RT:  $F(2,31)=6.04$ ,  $p=.0061$ ]. Averaging number of trials across the 16 sessions in the drug administration period, the pemoline group attempted the largest number of trials ( $M \pm SD$ :  $95.2 \pm 14.5$ ) followed by the placebo ( $82.2 \pm 17.92$ ) and methylphenidate ( $81.5 \pm 17.92$ ) groups (Duncan Multiple Range Test,  $p \leq 0.05$  for pemoline vs. both placebo and

**Table 1: Factors Affecting Performance During Sleep Deprivation  
(Significance on ANOVA)**

Task	Day (D)	Hour of Day (H)	D x H
1. Four-Choice RT			
A. Number Attempts	.0000	.0000	.0017
B. Correct RT	.0000	.0000	.0024
C. Incorrect RT	.0000	.0000	NS
D. Accuracy	.0000	.0011	NS
2. Matrix			
A. Number Attempts	.0000	.0000	.0000
B. Correct RT	.0000	.0032	.0003
C. Incorrect RT	.0000	.0001	.0006
D. Accuracy	.0001	.0000	NS
3. DSS			
A. Number Attempts	.0000	.0001	NS
B. Accuracy	.0004	.0246	.0729
4. Logical Reasoning			
A. Number Attempts	.0000	.0001	.0012
B. Accuracy	.0000	NS	NS
5. Addition			
A. Number Attempts	.0000	.0000	.0022
B. Accuracy	.0000	.0012	NS
6. Digit Span	NS	.0090	NS

**Table 2: Stimulant Effects On Performance During Sleep Deprivation  
(Significance on ANOVA)**

Task	(S)	(S x D)	(S x H)	(S x D x H)
<b>1. Four-Choice RT</b>				
A. Number Attempts	NS	NS	.0016	NS
B. Correct RT	NS	NS	.0689	NS
C. Incorrect RT	NS	NS	.0136	NS
D. Accuracy	NS	.0958	NS	.0102
<b>2. Matrix</b>				
A. Number Attempts	.0026	NS	NS	.0327
B. Correct RT	.0130	.0496	NS	NS
C. Incorrect RT	.0061	.0627	.0221	.0557
D. Accuracy	NS	NS	NS	NS
<b>3. DSS</b>				
A. Number Attempts	NS	NS	.0565	NS
B. Accuracy	NS	NS	.0966	NS
<b>4. Logical Reasoning</b>				
A. Number Attempts	.0690	NS	NS	NS
B. Accuracy	NS	.0187	NS	NS
<b>5. Addition</b>				
A. Number Attempts	NS	NS	.0160	NS
B. Accuracy	NS	.0866	NS	NS
<b>6. Digit Span</b>	NS	NS	NS	NS

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Note: All stimulant effects are positive (oppose sleep loss and/or circadian effects) except for accuracy measures on Logical Reasoning and Addition, where the S x D interaction is negative (drug effect synergistic with sleep loss). S = Treatment group (pemoline, 37.5 mg every 12 hr X 4 doses; methylphenidate, 10mg

TABLE 3: Post-hoc Analyses of the Hours of the Day on Which Stimulants Interact With Sleep Deprivation Comparisons Between Drug-Placebo and Drug-Drug groups (Duncan Multiple Range test;  $p \leq 0.05$ ).

TASK	Pemoline> Placebo	Pemoline< Placebo	Pemoline> Methylph	Pemoline< Methylph	Methylph> Placebo	Methylph< Placebo
<b>I. Matrix</b>						
1. Number Attempts	A. 0430,0745 1345,1630 B. 2230,0145 0430,1030 1345	A. 1030,1345 1630,1945 B. 2230,0145 1030,1345 1630	A. 1030 A. 1030,1630 1945 B. 2230,1030 1345	A. 1030 A. 1030,1345 1630,1945 B. 0430 1345,1630	A. 1030 A. 1030,1945 B. 2230,0145 1030,1345 1630	A. 1030 A. 1030,1945 B. 2230,0145 1030,1345 1630
2. Correct RT	A. 0745 RT B. 2230,0145 1345	A. 1030,1630 1945 B. 2230,1030 1345	A. 1030 A. 1030,1345 1630,1945 B. 0430 1345,1630	A. 1030 A. 1030,1945 B. 2230,0145 1030,1345 1630	A. 1030 A. 1030,1945 B. 2230,0145 1030,1345 1630	A. 1030 A. 1030,1945 B. 2230,0145 1030,1345 1630
3. Incorrect RT	A. 0745 B. 0145,0430 1345	A. 1030,1345 1630,1945 B. 2230,0145 1345,1630	A. 1030,1945 B. 0430 1345,1630	A. 1030,1945 B. 2230,0145 1030,1345 1630	A. 1030,1945 B. 2230,0145 1030,1345 1630	A. 1030,1945 B. 2230,0145 1030,1345 1630
<b>II. Addition</b>						
1. Number Attempts	A. 0145,0430, 0745,1030, 1345 B. 0430,0745	A. 0145,0430, 0745,1345 B. 0145,0430, 0745	A. 0145,0430, 0745,1345 B. 0145,0430, 0745	A. 0145,0430, 0745,1345 B. 0145,0430, 0745	A. 0145,0430, 0745,1345 B. 0145,0430, 0745	A. 0145,0430, 0745,1345 B. 0145,0430, 0745
2. Accuracy	B. 1630					

TABLE 3 (continued): Post-hoc Analyses of the Hours of the Day on Which Stimulants Interact With Sleep Deprivation. Comparisons Between Drug-Placebo and Drug-Drug groups (Duncan Multiple Range test;  $\alpha \leq 0.05$ ).

TASK	Pemoline> Placebo	Pemoline< Placebo	Pemoline> Methylph	Pemoline< Methylph	Methylph> Placebo	Methylph< Placebo
<b>III. Four-Choice RT</b>						
1. Correct	A. 0245, 0530 RT	B. 0530			A. 0530 B. 0530	
2. Incorrect	A. 0530 RT	B. 0245, 0530			B. 0530	
<b>IV. Logical Reasoning</b>						
1. Accuracy	A. 0530 Attempts	B. 1445			B. 0530 B. 0845	
2. Accuracy	A+B. 0245					
<b>V. DSS</b>						
1. Number	A. 0530 Attempts					
2. Accuracy	A+B. 0245					

Note: A = First 24-hour period (2230-2330) Tues - (1945-2045) Wed; B = Second 24-hour period (2230-2330) Wed - (1945-2045) Thurs; A+B = Data from the two days combined; Methylph = Methylphenidate.

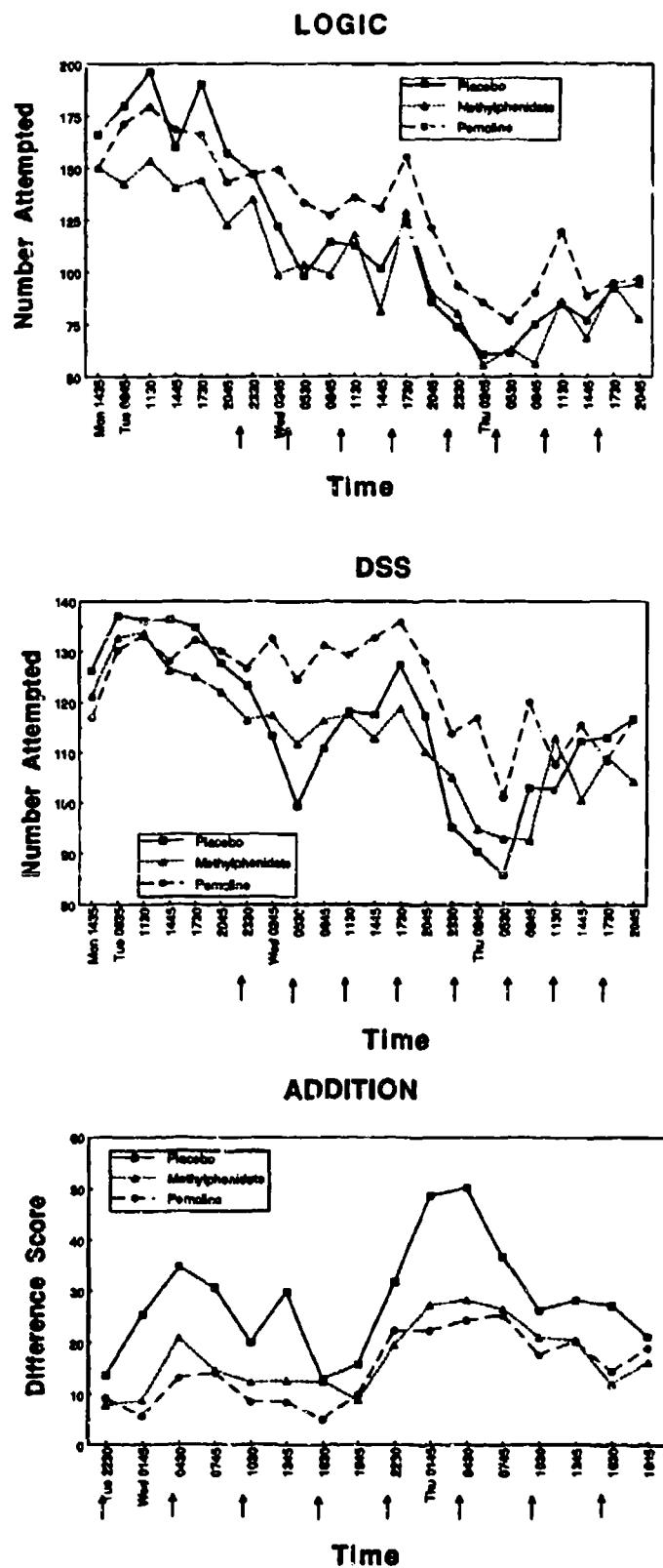


FIGURE 4: NUMBER ATTEMPTED GRAPHS

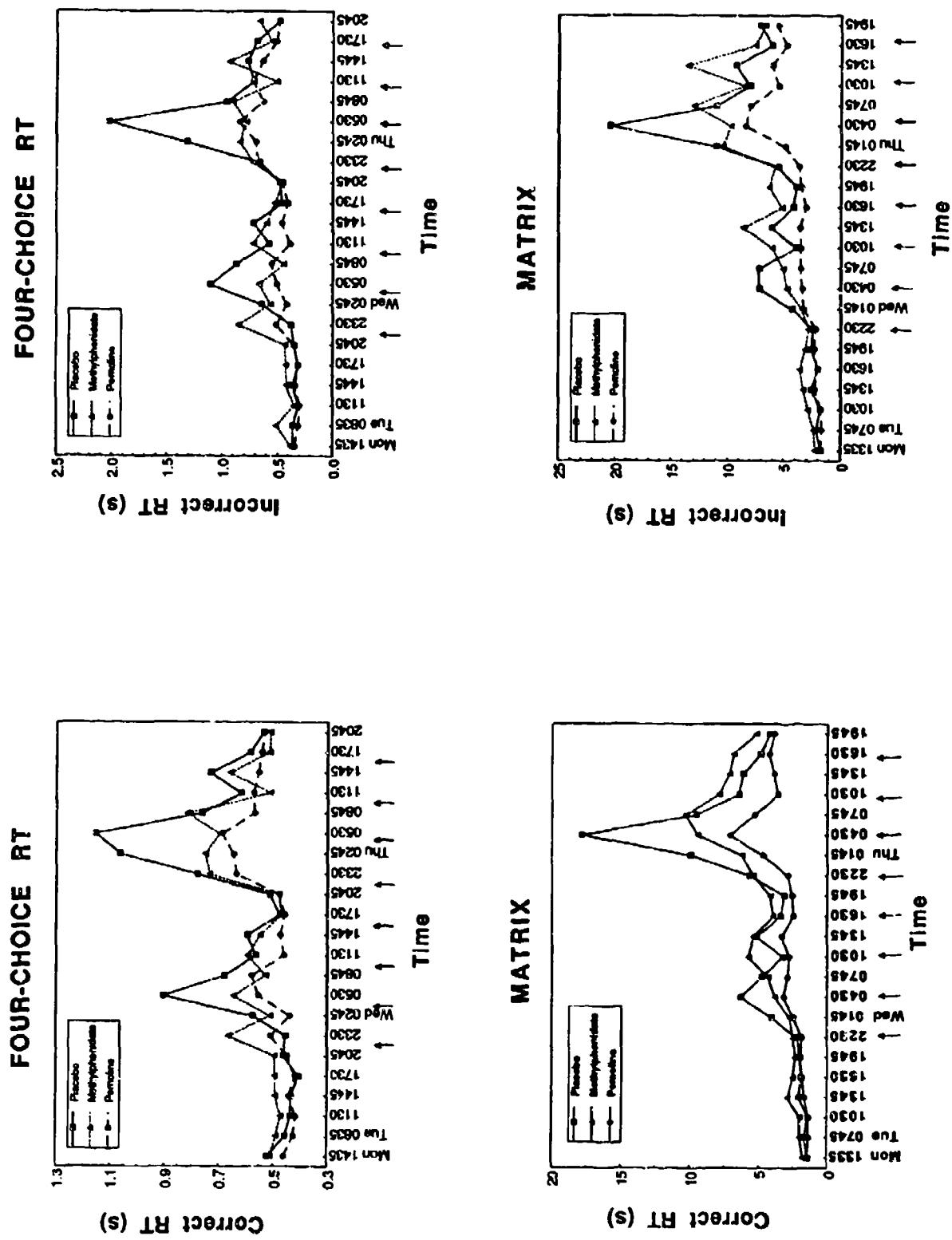


FIGURE 5: CORRECT AND INCORRECT RT GRAPHS

methylphenidate). The pemoline group also responded most quickly when correct, as well as when incorrect (correct RT:  $3.54 \pm 2.69$  s for pemoline,  $5.67 \pm 3.43$  s for methylphenidate, and  $6.03 \pm 5.9$  s for placebo; incorrect RT:  $4.54 \pm 3.10$  s for pemoline,  $7.31 \pm 4.58$  s for methylphenidate, and  $7.34 \pm 6.14$  s for placebo) (Duncan Multiple Range Test,  $p \leq .05$  for all pemoline vs. other group comparisons). There is a strong trend for a similar S effect on number of attempts in Logical Reasoning [ $F(2,31)=2.91$ ,  $p=.069$ ].

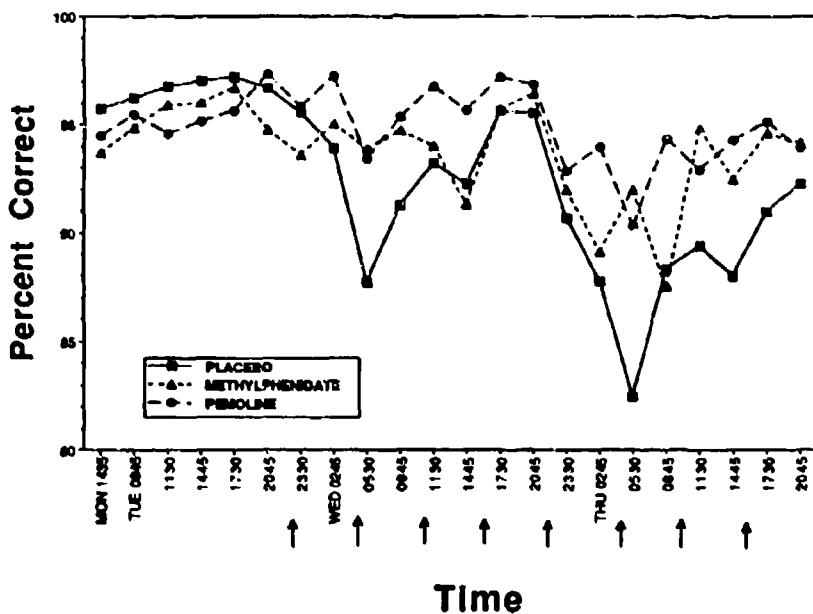
Matrix was also the only task showing an S x D interaction in response speed. Correct RT deteriorated less from D1 to D2 in the pemoline group (D2 mean - D1 mean: pemoline, 1.75; methylphenidate, 3.21; placebo, 4.06;  $F(2,31)=3.31$ ,  $p=.0496$ ). Among the other tasks, there were significant findings or trends for interactive effects of S x H for every speed measure except number attempted on Logical Reasoning (Digit Span had no speed measure). Most of these interactions related to the pemoline group working faster than the placebo and/or the methylphenidate groups (Figure 4, Table 3). These effects were most prominent around the time of the circadian trough (0100 hr to 0600 hr), particularly during the second night of sleep deprivation when the decrements in performance for the placebo group were most dramatic.

#### Drug Effects on Accuracy

Significant drug effects on accuracy are presented graphically in Figure 6. Four-Choice RT showed a significant positive S x D x H interaction [ $F(9.24,147.26)=2.16$ ,  $p=.0102$ ] and a trend for a positive S x D [ $F(2,32)=2.53$ ,  $p=.0958$ ] interaction. Post hoc tests showed pemoline subjects to be more accurate in Four-Choice RT than placebo subjects at 0530 hr on D1 and at 1450 hr on D2. The DSS showed a trend for a positive S x H interaction [ $F(5.35,82.86)=1.91$ ,  $p=.0966$ ]. In DSS there were large differences in accuracy between the pemoline and placebo groups during the second circadian low period; however, the pemoline group had very high standard deviations during that period, so no significant group differences were found by post hoc testing on individual trials. When trials for the same time of day on the two different days were combined, the pemoline group showed higher accuracy than the placebo group at 0245 hr.

The Logical Reasoning task showed a significant S x D interaction on accuracy [ $F(2,31)=4.54$ ,  $p=.0187$ ]. In Figure 6, it is apparent that subjects receiving pemoline tend to

## FOUR-CHOICE



## LOGIC

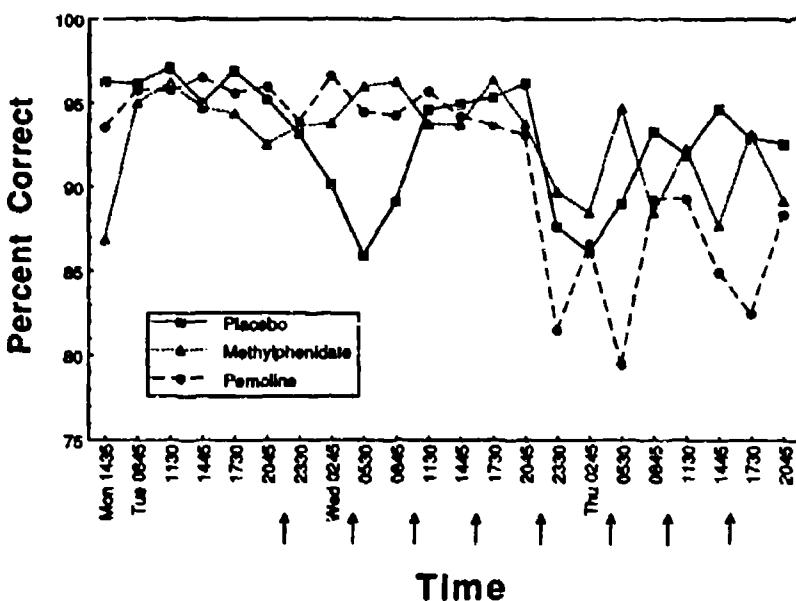


FIGURE 6: ACCURACY GRAPHS

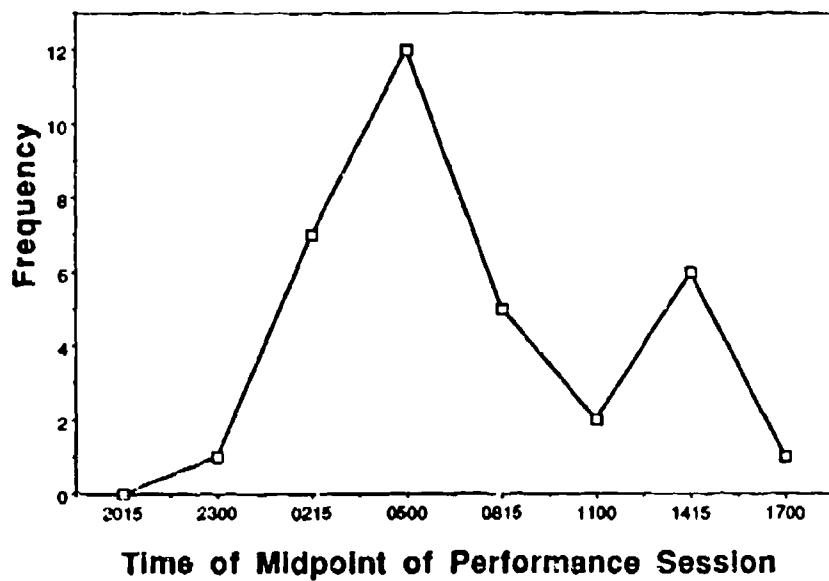
do better the first day but worse the second night.

The post hoc analyses (Table 3) revealed no significant drug accuracy effects during the first circadian cycle in the sleep deprivation period. However, at 0530 hr during the second circadian low period, the pemoline group accuracy dropped below that of both the placebo and the methylphenidate groups (Table 3). The pemoline group was also significantly less accurate than the placebo group the following afternoon at 1445 hr (Table 3). Addition showed a trend for a negative S x D interaction [ $F(2,31)=2.65$ ,  $p=.0866$ ]. Post hoc tests showed pemoline subjects to be less accurate than placebo subjects at 1630 hr on D2 (Table 3). Matrix and Digit Span showed no drug effects on accuracy.

#### Timing of Drug Effects

Figure 7 shows a frequency distribution of the hours of the day (combining D1 and D2) on which the pemoline group showed significant differences from the placebo group on any performance measure. The times represent the midpoint of the performance session. For example, the number of interactions at 0145 hr and 0245 hr are combined and shown at 0215 hr. This plot demonstrates an apparent circadian pattern to pemoline's effects. Results from the sleep questionnaires filled out at baseline and again after the recovery sleep showed no evidence of pemoline interfering with the recovery sleep, despite its long half-life.

**FIGURE 7: TIME OF DAY OF SIGNIFICANT DIFFERENCES BETWEEN PEMOLINE AND PLACEBO GROUPS**



## DISCUSSION

### Vital Signs, Sleepiness and Mood

Although there were statistically significant drug effects on vital signs, the effects were small and probably of no clinical significance. All measures remained well within normal limits. Methylphenidate has previously been found to increase pulse and stimulate the cardiovascular system (Coons et al., 1981; Evans, Gaultieri, & Hicks, 1986; Gaultieri, Hicks, Levitt, Conley, & Schroeder, 1986). At the dose level employed in this study, methylphenidate had no significant effect on either blood pressure, pulse, or temperature. The dose of pemoline used in this study caused small elevations in diastolic blood pressure. The mean diastolic blood pressure during the drug administration period was 66.7 mmHg in the pemoline group, 61.25 mmHg in the methylphenidate group and 62.5 mmHg in the placebo group. There was no evidence of any drug effect on systolic blood pressure, mean blood pressure, or rate pressure product. Subjects receiving pemoline showed slightly higher pulse rates than subjects receiving methylphenidate, but not significantly higher pulse rates than subjects receiving placebo. Connors and Taylor (1980) also reported no pulse or blood pressure effect with moderate doses of either pemoline or methylphenidate. Thus, at these doses and administration schedules, we have found no evidence that either drug has significant cardiovascular effects. However, this is too small a sample to rule out the possibility of such effects, particularly because no exercise was performed by the subjects.

Moderate doses of pemoline significantly reduced levels of sleepiness as measured both subjectively and objectively. This occurred primarily through a reduction in the increased sleepiness measured during the early morning and afternoon hours. Pemoline significantly reduced subjective sleepiness throughout the 48-hr period over which drugs were administered. As measured by the tapping task, however, pemoline was significantly effective in reducing sleepiness only for 32 hr after the drug was first administered (i.e., until the 48th hr of sleep deprivation). Methylphenidate was not effective in reducing sleepiness on either the subjective or objective measures.

Given pemoline's marked effect on performance and on sleepiness, its lack of an effect on mood as measured by the POMS is of interest. Other studies involving stimulants and sleep

loss have found significant correlations between performance and mood. Newhouse et al., (1989) found that 10-mg and 20-mg doses of amphetamine produced significant (although short-lived) differences, as compared to placebo, on the Vigor-Activity and Fatigue-Inertia subscales of the POMS after 48 hr of sleep loss.

The dose of pemoline used in this study is moderate. The finding of Newhouse et al. (1989) that amphetamine altered mood during sleep deprivation was dose dependent. Perhaps a higher dose of pemoline would produce significant effects on the POMS. The changes seen on the subjective sleepiness measure, the VAS, do indicate some mood effect. Previous reports have suggested that visual analogue scales are more sensitive to drug effects than Likert-type scales such as the POMS (Grant et al., 1991).

### Performance

The results of sleep deprivation in the placebo group agree with previous studies of sleep loss. There was a significant reduction in response speed and accuracy on a variety of cognitive tasks during 64 hr without sleep accompanied by a strong underlying circadian rhythmicity. The circadian variations might have been decreased if we had blocked time cues by preventing access to windows. However, as most military environments include such cues, their presence may make our results more operationally applicable. Of the two drugs, only pemoline showed consistent effects. A fourth of the significant differences between the methylphenidate and placebo groups involved instances when methylphenidate subjects performed worse than the placebo subjects (Table 3). These were standard medical doses and, as such, conservative administration for stimulant effects. It is possible that methylphenidate might show more benefit at a higher dose. The present discussion, however, will focus on the pemoline results.

Subjects performed significantly faster with pemoline than with placebo during one or more sessions on five of the six tasks reported in this paper. Pemoline's beneficial effect on speed in cognitive tasks is consistent with typical stimulant effects. The first night, pemoline effectively eliminated the usual circadian drop in speed in most tasks. Performance speed dropped somewhat during the second night at the circadian nadir (0000 hr - 0600 hr) in all groups, but less in the pemoline group than in the placebo group.

Overall, the effect on accuracy differed from that on speed. Two tasks (Digit Span and

Matrix) showed no evidence of drug effects on accuracy. Four-Choice RT showed a significant beneficial effect on accuracy with pemoline and DSS showed a trend for a beneficial effect. The Logical Reasoning task appeared to show a synergistic interaction between pemoline and the effects of sleep deprivation. There was an S x D interaction manifested by lower accuracy in the pemoline as compared to the placebo group starting during the second circadian low period. The Addition task also showed a synergistic trend for pemoline interacting with sleep loss.

The differences between the effect of pemoline on speed and on accuracy could result from differential interaction of the drug with stimulus and response components of the tasks. Sleep loss probably has general negative effects on both stimulus and response processing. It has been suggested that, in general, stimulants selectively interact with response processing, response selection, and response speed (Callaway, 1983). This could explain the overall tendency to produce more or faster responses with pemoline administration. Facilitation of response processing might also maintain other performance measures in tasks where response processing is the major component. In DSS, the stimulus is a single digit whereas the response must be selected from a somewhat complex table. Thus, facilitation of response processes by pemoline might explain the trend to counteract degradation in both speed and accuracy. However, where the stimulus component is maximal and the response component minimal, accuracy may not be maintained as well.

This interpretation of the data does not explain why pemoline would have a deleterious effect on performance accuracy. It is difficult to explain this result as a speed-accuracy trade-off phenomenon when (a) the only task with a significant decrease in accuracy (Logical Reasoning) did not show a significant increase in speed and (b) those tasks with the most increase in speed showed no accuracy changes.

The literature suggests that methylphenidate and pemoline have the most beneficial effect on performance in cognitive tasks requiring sustained attention (e.g., vigilance) or concentration over relatively long periods of time. Stimulants enhance performance in tedious discrimination or rote learning (Peloquin & Klorman, 1986; Rapoport et al., 1980). Concentration is reportedly improved with methylphenidate (Coons et al., 1981) or pemoline, although the latter may be dose dependent because there are some reports of deterioration of concentration at higher doses (Haward, 1970). The studies generally seem to agree that the drugs reduce the number

of errors of omission in continuous attention or vigilance tasks (see, e.g., Coons et al., 1981; Dureman, 1962; Herbert, Gelfand, Clark, & Gelfand, 1968; Orzack et al., 1968; Peloquin & Klorman, 1986; Talland, 1970). There is, however, a lack of agreement regarding the reduction of errors of commission, especially when the drugs interact with another variable, such as health or age (e.g., Halliday et al., 1986; Peloquin & Klorman, 1986; Strauss et al., 1984). The most attention-dependent task in the present study, Matrix, where even a brief lapse in attention can leave the subject with no alternative other than a blind guess about the response, showed no accuracy effects with either drug. However, the Matrix task involves spatial discrimination and memory as well as attention. These other factors might have obscured any stimulant effect on attention.

There are fewer definitive or consistent reports regarding the effects of either of these stimulants on cognitive tasks in which attention is not the major component. Several studies report improvement in accuracy and response speed with the administration of methylphenidate in tasks designed to test short-term memory or memory scan<sup>2</sup> (e.g., Brumaghim et al., 1987; Coons et al., 1981; Peloquin & Klorman, 1986; Talland, 1970). Other recent studies found that methylphenidate improves speed but not accuracy in memory scan (Fitzpatrick et al., 1988) or is ineffective altogether (Halliday et al., 1986). An earlier study reported no effects of pemoline (37.5 mg) on short-term memory (Smith, 1967). In the present study, the tasks showing a trend toward positive accuracy effects with pemoline do not have memory as a major component. For example, the table of codes for DSS is constantly present to be referred to, and the individual problem remains displayed on the screen until the subject chooses to respond. Overt verbal processing probably plays a major role in Logical Reasoning. Both methylphenidate and pemoline improved the performance IQ scores (e.g., the Harris-Goodenough Draw-A-Man test and the performance scale of the WISC), but not the verbal IQ scores of children diagnosed as suffering from minimal brain dysfunction (Conners & Taylor, 1980). A single daytime dose of 37.5 mg of pemoline in non-sleep-deprived normal subjects was reported to affect performance adversely on a verbal learning task (Smith, 1967). If this negative interaction applies to verbal processing in general, it could explain the negative effects on Logical Reasoning accuracy. However, the trend toward a positive effect during the first circadian nadir (Figure 6) argues against a general negative interaction of pemoline with verbal processing.

Another possible factor in pemoline's differential effects on accuracy relates to dose response relationships. The interaction of a stimulant drug with cognitive function may not be unidirectional at all doses. For most drug effects, the dose response relationship is an inverted U with an increase in positive effect to an optimum dose level, followed by a decreasing positive effect and even negative effects as dose increases (Callaway, 1983). Furthermore, various cognitive functions may be differentially sensitive to drug dosage and their optima may occur at different dose levels. There is evidence that some types of cognitive performance may benefit from high levels of pemoline (Gelfand et al., 1968; Orzack et al., 1968), whereas other tasks get optimum benefit at lower doses and may deteriorate at high doses (Haward, 1970). The cognitive functions involved in Four-Choice RT may have a relatively high optimum level so that the accumulated drug level by the second night of sleep loss (3 doses of 37.5 mg each, over a 24-hr period) still results in a positive interaction. The optimum dose response level of pemoline for Logical Reasoning may be lower, so that the accumulated level of pemoline by the second night of sleep loss exceeds the optimum. An excessive drug level could serve to exacerbate the performance accuracy deterioration resulting from accumulated sleep loss and the effects of the circadian nadir, producing poorer performance in the pemoline group than in the other groups. It is possible that lower doses of pemoline or a different administration schedule might interact positively and ameliorate the effects of sleep loss on Logical Reasoning. A study involving other verbal tasks as well as a different administration schedule and varying dose levels is planned to test these hypotheses.

It does seem clear that time of day is much more important than duration of sleep deprivation in determining pemoline's effects. In the frequency distribution of pemoline's effects (Figure 7), a large peak at the circadian nadir is apparent, with a smaller secondary peak in the early afternoon. The distribution may, therefore, be bimodal. The predominance of stimulant-circadian interactions is probably at least partially due to the fact that the circadian decrements in performance are larger than the monotonic sleep loss related decrements. Thus, if pemoline causes a moderate percentage reduction in either type of decrement the effect might only be apparent with the larger circadian deficits, given the overlay of other sources of variation (e.g., individual differences). An additional factor may be the contribution of drug blood levels. Pemoline should take about 2-4 hours after administration to reach peak blood

levels with peak central nervous system (CNS) stimulant effects occurring at around 8 hr with a half-life of 12 hr (Barnhart, 1992). Therefore, the dose at 2200 hr would peak around 0000 hr - 0200 hr, and the level will not have dropped much by 0500 hr. The smaller peak at 1415 hr (4 hr after administration) may represent drug effect without the interactive factor of the circadian low. Unfortunately, we do not have blood concentration levels of the stimulants to verify or reject this speculation. Two o'clock in the afternoon is also about the time of a lesser circadian low known as the "post-lunch dip."

Certainly, the duration of sleep deprivation should not be the only determinant of whether or when to administer pemoline for performance maintenance. An individual deprived of sleep for 50 hr will probably not benefit much from pemoline administered at 1000 hr, whereas one with minimal sleep deprivation might well benefit at 0200 hr if pemoline is administered at 2200 hr. Our data suggest that pemoline predominantly affects decrements due to the circadian cycle, with prior hours of wakefulness contributing as an additive factor. It is uncertain whether this finding can be generalized to other stimulants. If it can, then previous sleep deprivation studies, which have administered stimulants after sleep deprivation, but at times distant from the circadian low point (Newhouse et al., 1989), may have underestimated potential stimulant benefits. Some data suggest that not all stimulants behave in this manner. P. Gillooly (personal communication, May 10, 1990) found greater performance benefits with dextroamphetamine when it was administered in the morning than at night. However his subjects were not sleep deprived.

The predominant interaction with the circadian rhythmic factor rather than with the monotonic 'fatigue' factor suggests that it might be preferable to administer pemoline only at night rather than around the clock. It is hypothesized that pemoline's long half-life would protect from rebound fatigue problems during the day following nighttime administration.

## FOOTNOTES

1. To be able to define clearly the sleep deprivation and circadian effects on the performance tasks, it was critical that they always be presented in exactly the same order. Otherwise, these effects would have been confounded by administration order effects. It is possible that the negative effect of pemoline on Logical Reasoning accuracy would not have been seen if Logical Reasoning had not been administered near the end of the performance battery. We cannot rule this out. The question of whether other tasks would have shown similar effects if they had been presented late in the testing sequence does remain open. However, the tasks that were presented immediately before Logical Reasoning showed no trace of such an effect.

2. Memory scan was tested by a modified Sternberg test (Sternberg, 1969). Subjects memorized a novel memory set of two or four consonants before each block of trials. After demonstrating recall, the subject was presented with 80 trials on each of which four consonants were presented simultaneously. Subjects were required to respond whether one of the four letters was a member of the memory set, and if so, to identify it.

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